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(21) Application No. : 31399/84 (22) Application Date : 01.08.84

(30) Priority Data

(31) Number	(32) Date	(33) Country
3327856	02.08.83	DE FEDERAL REPUBLIC OF GERMANY
3336197	05.10.83	DE FEDERAL REPUBLIC OF GERMANY

(43) Publication Date : 11.09.86

(44) Publication Date of Accepted Application : 26.11.87

(71) Applicant
HOECHST A.G.;

(72) Inventor
NAME NOT GIVEN

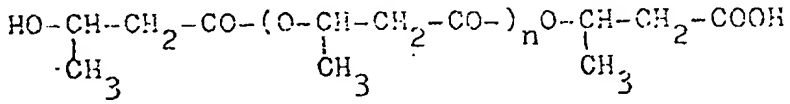
(74) Attorney or Agent
EDWD. WATERS & SONS

(54) Title
PHARMACEUTICAL PRODUCTS WITH PROTRACTED RELEASE WHICH CONTAIN REGULATORY PEPTIDES

(57) IMPLANT INCLUDES TABLETS, FLAKES AND INJECTIONS.

Claim

1. An implant containing a regulatory peptide or one of its analogs as the active compound and naturally occurring poly-D(-)-3-hydroxybutyric acid of the formula



in which n represents a number from ~~between~~ 500 to ~~and~~ 25,000, as the biologically degradable carrier.

(CONVENTION. By one or more persons and/or a Company.) Form 4

567572

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

CONVENTION APPLICATION FOR A PATENT

(1) Here insert (in full) Name or Names of Applicant or Applicants, followed by Address (es).

I/We (1) HOECHST AKTIENGESELLSCHAFT,
of 45 Bruningstrasse,
D-6230 Frankfurt am Main 80,
Federal REpublic of Germany.

(2) Here insert Title of Invention.

hereby apply for the grant of a Patent for an invention entitled: (2)
PHARMACEUTICAL PRODUCTS WITH PROTRACTED RELEASE WHICH CONTAIN REGULATORY PEPTIDES, AND PROCESSES FOR THEIR PREPARATION.

(3) Here insert number(s) of basic application(s)

(4) Here insert Name of basic Country or Countries, and basic date or dates

which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered (3)
P 33 27 856.3 and P 33 36 197.5
for a patent or similar protection made in (4) Federal Republic of Germany on 2nd August, 1983 and 5th October, 1983.

[illegible] 15-10-87

My/Our address for service is Messrs. Edwd. Waters & Sons, Patent Attorneys, 50 Queen Street, Melbourne, Victoria, Australia.

LODGED AT SUB-OFFICE
- 1 AUG 1984
Melbourne

DATED this 19th day of July, 1984

(5) Signature (s) of Applicant (s) or Seal of Company and Signatures of its Officers as prescribed by its Articles of Association

(5)
HOECHST AKTIENGESELLSCHAFT
James Murray
JAMES MURRAY

Form 8

COMMONWEALTH OF AUSTRALIA

Patents Act 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION UNDER PART XVI. FOR A PATENT.

In support of the Convention application made under Part XVI. of the Patents Act 1952 by HOECHST AKTIENGESELLSCHAFT of 45, Brüningstrasse, D-6230 Frankfurt/Main 80, Federal Republic of Germany for a patent for an invention entitled:
"PHARMACEUTICAL PRODUCTS WITH PROTRACTED RELEASE WHICH CONTAIN REGULATORY PEPTIDES, AND PROCESSES FOR THEIR PREPARATION"

We, Karl-Hermann Meyer-Dulheuer, 31 Höhenstraße, D-6242 Kronberg/Taunus, Otto Klein, 24 Johann-Strauß-Straße, D-6233 Kelkheim (Taunus); Federal Republic of Germany
do solemnly and sincerely declare as follows:

1. We are authorized by HOECHST AKTIENGESELLSCHAFT the applicant for the patent to make this declaration on its behalf.

2. The basic applications as defined by Section 141 of the Act ~~was~~ were made in the Federal Republic of Germany under No. P 33 27 856.3 on August 2, 1983 and under No. P 33 36 197.5 ~~by HOECHST AKTIENGESELLSCHAFT~~ on October 5, 1983 by HOECHST AKTIENGESELLSCHAFT

3. a) Wolfgang König, 25 Eppsteiner Straße, D-6238 Hofheim am Taunus
b) Heinz-Rüdiger Seidel, 15 Im Kirschenfeld, D-6370 Oberursel/Taunus
c) Jürgen Kurt Sandow, 22 Am Haideplacken, D-6240 Königstein/Taunus
a) - c) Federal Republic of Germany

~~is~~ are the actual inventor(s) of the invention and the facts upon which HOECHST AKTIENGESELLSCHAFT is entitled to make the application are as follows:
The said HOECHST AKTIENGESELLSCHAFT is the assignee of the said Wolfgang König, Heinz-Rüdiger Seidel and Jürgen Kurt Sandow

4. The basic applications referred to in paragraph 2 of this Declaration ~~was~~ were the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Frankfurt/Main, Federal Republic of Germany
this 16th day of July 1984

To the Commissioner of Patents

Hoechst Aktiengesellschaft

ppa. Meyer-Dulheuer i.V. Klein

Prokurist Authorized signatory

PAT 510 (ppa.Meyer-Dulheuer) (i.V.Klein)

567572

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

31399/84

Priority :

Related Art :

Name of Applicant : HOECHST AKTIENGESELLSCHAFT

Address of Applicant : 45 Bruningstrasse, D-6230 Frankfurt/Main 80, Federal REpublic of Germany.

Actual Inventor:

Address for Service : EDWD. WATERS & SONS,
50 QUEEN STREET, MELBOURNE, AUSTRALIA, 3000.

Complete Specification for the invention entitled:

PHARMACEUTICAL PRODUCTS WITH PROTRACTED RELEASE WHICH CONTAIN REGULATORY PEPTIDES, AND PROCESSES FOR THEIR PREPARATION

The following statement is a full description of this invention, including the best method of performing it known to :- US

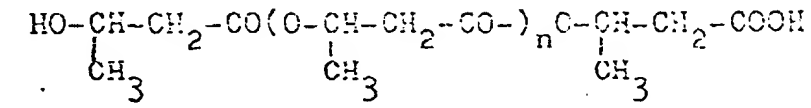
The invention relates to a formulation, which can be implanted, of regulatory peptides and of analogs thereof with protracted release, and to processes for the preparation of the implants.

It has already been reported that, during in vitro experiments, the active compound is released slowly from matrix tablets containing 7-hydroxyethyltheophylline, as the active compound, and poly-D(-)-3-hydroxybutyric acid, as the biologically degradable carrier material (Pharm. Ind. 45, pages 525-527 (1983)).

It has furthermore been reported that the peptides are released slowly from medicaments containing peptides as the active compounds and biodegradable polymers as carrier substances. The carriers are chiefly synthetic polyesters of lactic acid and copolymers of lactic acid and glycolic acid (c.f. for example, European Patent Applications publication numbers 0,052,510 and 0,058,481) and synthetic amino acid polymers (c.f. U.S. Patent 4,351,337). The disadvantage of synthetic polymers is that residues of the polymerization catalyst must be reckoned with. Such residues are undesirable in medicaments, especially in implants.

It has now been found that naturally occurring polyhydroxybutyric acid is suitable as a carrier for peptide-containing implants from which the active compound is released in a protracted manner.

The invention thus relates to implants containing regulatory peptides or analogs thereof as the active compounds and neturally occurring poly-D-(-)-3-hydroxybutyric acid (PHB) of the formula



in which n represents a number ~~between~~ from 500 ~~and~~ to 25,000, as the biologically degradable carrier.

In the statements made above and below, "peptides" means regulatory peptides and analogs thereof, as well as physiologically acceptable salts thereof.

The invention furthermore relates to processes for the preparation of implants containing regulatory peptides or analogs thereof as active compounds, which comprise

1. dissolving the active compound in a low-molecular alcohol which has 1 to 4 carbon atoms and is optionally substituted by up to 3 fluorine atoms or in water or in a mixture of these solvents, mixing the solution with the poly-D-(-)-3-hydroxybutyric acid, drying the moist material and pressing the product, or

2. dissolving the poly-D(-)-3-hydroxybutyric acid in a halogenated aliphatic C_1-C_4-hydrocarbon, mixing the solution with a solution of the active compound in a low-molecular alcohol which has 1 to 4 carbon atoms and is optionally substituted by up to 3 fluorine atoms, subjecting the resulting solution to spray-drying and

pressing the dried cottonwool-like material, or

3. dissolving the poly-D(-)-3-hydroxybutyric acid in a halogenated aliphatic C_1-C_4-hydrocarbon, suspending the active compound in this solution, pouring the suspension onto a suitable substrate, for example into a glass dish, evaporating off the solvent and, if appropriate, dividing up the resulting film into pieces of suitable size.

The resulting pressed pieces or films can be ground and divided into various particle sizes by sieving. The solid shaped articles can be implanted as such or, after prior comminution, injected in the form of suspensions.

The regulatory peptides (naturally occurring, synthetic and semi-synthetic), which can also be used in the form of salts, are soluble in water and low-molecular alcohols which are optionally substituted by fluorine. Possible alcohols are, in particular, methanol and trifluoroethanol. Particularly suitable solvents for the PHB are fluorinated and chlorinated hydrocarbons, such as methylene chloride, chloroform and 1,1,2-trichloro-1,2,2-trifluoroethane, methylene chloride and chloroform being especially suitable.

The PHB is synthesized by bacteria, such as, for example, by Alcaligenes eutrophus. It is obtained in the form of small globules in the bacteria and can be greatly increased in concentration by corresponding conditions in the bacteria and easily isolated therefrom (c.f. Pharma.

Ind. 45, pages 525-527). Each unit of PHB consists of optically pure D-(-)-3-hydroxybutyric acid.

Biological degradation of PHB in vivo proceeds relatively slowly and contributes little to the release of an active compound from an implant. The release is chiefly controlled by the surface of the implant and the amount of active compound contained therein. If very small amounts of a peptide are to be released for a relatively long time, an impant with a small surface area and a low peptide content, for example in the form of pressed pieces, is advisable. The release from the pressed piece can be further reduced by coating the implant completely or partly with a layer of PHB or other biologically degradable polymers, such as polylactic acid or polylactic acid/polyglycolic acid copolymers or with polymers such as ethylcellulose, poly(meth)acrylic acid derivatives or polydimethylsiloxanes.

An essentially uniform release of peptides for up to one year can be achieved with such impants. The implants can easily be removed by operation, if the treatment is to be discontinued.

Whilst the implantation tablets prepared according to method 1 release a relatively constant amount of a regulatory peptide from the start, the implants obtained according to method 2 release a relatively large amount of peptide in the first days and then release constant small amounts. Good adaptation to the desired pattern of release of the active compound is thus possible with the

implants according to the invention.

These slow rates of release are surprising when compared with the rates of release of about 40 days, which in contrast are rapid, obtained with the copolymers of lactic acid and glycolic acid (c.f. European Patent Application publication number 0,058,481).

Very small tablets or other small shaped articles throughout which the entire dose is distributed are suitable as implants for shorter release times. As a result of the substantially larger surface area which a large number of medicinal carriers have in comparison with a single shaped piece, the release is more rapid. Small particles which can be prepared by comminution of tablets and films are preferred. They can be injected, after suspension in a suitable medium. The particle size should not exceed a particular value here and is advantageously in the range from 0.1 to 200 µm.

Physiological saline solution in which, for example, 1% of hydroxypropylmethylcellulose (Methocel R E5), carboxymethylcellulose (Blanose R 7LF) or polyethylene glycol sorbitan monostearate (Tween R 20) is dissolved can be used for suspension and injection of the particles.

Regulatory peptides are endogenous peptides which have a physiological action, they are also called peptide hormones, which, depending on the site of synthesis or release, are classified into, for example, peptide hormones of the hypothalamus, of the pituitary gland, of the

gastrointestinal tract or of the thyroid gland. This classification is inappropriate today, since it is known that the so-called peptide hormones are not produced only at one site in the body and, in addition to their endocrine mode of action, can also act in a paracrine or neurocrine manner.

Classification of these peptides according to indications is also inappropriate, since they can develop the most diverse therapeutic activities, depending on the site of action and the dose.

Examples of representative regulatory peptides which the implants according to the invention can contain are oxytocin, vasopressin, thyroliberin the anorexigenic peptide, gonadoliberin, calcitonin, parathormone the epidermal growth factor, secretin the vasoactive intestinal peptide, somatoliberin the gastrin-inhibiting or glucose-dependent insulinotropic peptide, glucagon the pancreatic spasmolytic peptide, somatostatin, bombesin the gastrin-releasing peptide, motilin, neutrotensin, substance P, sauvagin, corticoliberin, urotensin I and II, angiotensin I and II, bradykinin, corticotropin, encephalins, dynorphin, dermophin, casomorhins, gastrin, cholecystokin, cerulein, thymus factors, interferons, insulin, growth hormone and prolactin.

The highly active analogs of gonadoliberin, such as, for example, [D-Ser(Bu^t)^6]gonadoliberin-(1-9)nonapeptide-ethylamide (buserelin, Drugs of the Future 4, 1979, pages 175-77, 8, 1983, page 254), [D-Trp^6]

gonadoliberin (Drugs of the Future 3, 1978, pages 645-646), [D-Trp^6]gonadoliberin(1-9)-nonapeptide-ethylamide (Drugs of the Future 7, 1982, pages 637-642), [D-Leu^6] gonadoliberin(1-9)-nonapeptide-ethylamide (Drugs of the Future 7, 1982, pages 882-886), [D-Ser(But)^6, AzaGly^{10}] gonadoliberin (Drugs of the Future 5, 1980, pages 191-192; 8, 1983, pages 364-365), [D-Trp^6, N-MeLeu^7] gonadoliberin-(1-9)-nonapeptide-ethylamide (Drugs of the Future 8, 1983, pages 347-350), [D-α-aminoadipic acid δ-tert.-butyl ester^6] gonadoliberin-(1-9)-nonapeptide-ethylamide (German Offenlegungsschrift 3,020,941), [D-Lys(Boc)^6] gonadoliberin-(1-9)-nonapeptide-ethylamide (German Patent 2,438,350), [D-3-(2,4,6-trimethylphenyl)-Ala^6] gonadoliberin and [D-3-(2-naphthyl)-Ala^6] gonadoliberin (J. Med. Chem. 25, 1982, pages 795-801), are of particular importance.

In a high dosage, these peptides reduce the plasma levels of lutropin and follitropin and hence those of the gonadal steroids testosterone and oestradiol. These derivatives can therefore be used for hormone-dependent tumors, such as, for example, carcinoma of the prostate or of the breast, and also for endometriosis and pubertas praecox in children. Continuous uniform release of the active compound is particularly important for this therapy. With the formulation according to the invention, the necessary amount of the active compound, which would otherwise have to be administered parenterally or intranasally 2-3 times daily, can be released for weeks or months with a single administration. Use on older persons

and children is thus particularly safe from administration errors (compliance).

Another important use of the formulation according to the invention is the protracted release of somatostatin and somatostatin analogs, which can be used in all cases where somatostatin infusions exhibit an advantageous effect; for example for hemorrhages of the gastrointestinal tract, for gastric ulcers, for the treatment of tumors which produce hormones which can be inhibited by somatostatin, such as, for example, for Zollinger-Ellison syndrome or Verner-Morrison syndrome, or for tumors which produce insulin or glucagon, for hormone-dependent tumors, if the corresponding hormones can be inhibited by somatostatin, for certain types of leukemia, for metabolism disorders with increased hormone levels which can be inhibited by somatostatin, such as, for example, rheumatoid arthritis, where the plasma insulin and growth hormone are too high, for acromegaly or psoriasis, for Diabetes mellitus (inhibition of glucagon), for chondrosarcoma and for states of shock.

Highly active analogs of somatostatin are compounds in which, for example, Trp^8 is replaced by D-Trp or 5-F-D-Trp, or shortened cyclic compounds, such as, for example,

(Nature 292, 1981, page 55) or

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol

(Life Sci. 31, 1982, pages 1,133-1,140).

Therapy of upper gastrointestinal hemorrhages with secretin infusions can also be simplified by the new galenical formulation.

The ratio of active compound to carrier material can vary within wide limits. Since the peptides are administered in low dosages, the amount of carrier material in the implants is relatively high (for example 100 : 1 to 10,000 : 1).

Example 1:

2.5 g of PHB were moistened with a methanolic solution containing 2.875 mg of buserelin acetate (corresponding to 2.5 mg of buserelin) and mixed thoroughly. The moist material was dried in vacuo, with shaking. The procedure was repeated several times with pure methanol. The dry mixture was pressed to tablets (implants) weighing 50 mg and containing 50 µg of buserelin.

Example 2:

2.875 mg of buserelin acetate (corresponding to 2.5 mg of buserelin) were dissolved in 30 ml of methanol, and 2.5 g of PHB were dissolved in 70 ml of chloroform. The two solutions were combined and subjected to spray-drying. A flaky powder was obtained, from which tablets weighing 50 mg and containing 50 µg of buserelin were pressed.

Example 3:

The pressed pieces prepared under Example 1 or 2 were micronized. The resulting particles were divided into particle size ranges up to about 200 µm by sieving. The fractions were suspended in physiological saline solution with 1% of carboxymethylcellulose in a concentration of 50 mg/ml for injection.

Example 4:

2.5 g of PHB were dissolved in 25 g of chloroform. 287.5 mg of buserelin acetate (corresponding to 250 mg of buserelin) were suspended in this solution. The suspension was poured into a Petri dish. The solvent was allowed to evaporate slowly. A film was formed, and divided into flakes 1 cm^2 in size, containing about 5 mg of buserelin.

Example 5:

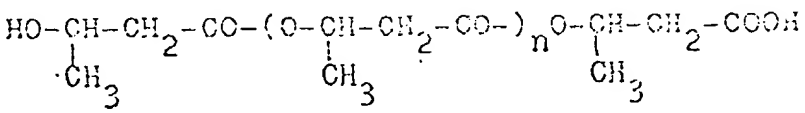
Biological testing of the formulations on rats

Two implantation materials of PHB and a copolymer of lactic acid and glycolic acid (PLG) of identical weight and size which had been prepared analogously to Example 1 were investigated. The materials were tested on adult rats weighing 400 g, the amount of peptide released each day being determined by pharmacokinetic detection by means of specific radioimmunoassay. In the case of the PHB implant, a release of 0.203 ± 0.038 ng of buserelin per day was found. In contrast, a release of 1.075 ± 0.029 ng of buserelin/day was found for the PLG implant. The total duration of the release of the peptide

was calculated from the cumulative rate of release. It is 221 ± 29 days for the PHB implant and 46.5 ± 1.2 days for the PLG implant. The PHB implant material is thus considerably more suitable for long-term release of peptides than the copolymer of lactic acid and glycolic acid (50:50) used for comparison.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An implant containing a regulatory peptide or one of its analogs as the active compound and naturally occurring poly-D(-)-3-hydroxybutyric acid of the formula



in which n represents a number from 500 to 25,000, as the biologically degradable carrier.

2. Implant as claimed in claim 1, which contains buserelin(acetate) as the active compound.

3. A process for the preparation of an implant as claimed in claim 1, which comprises

1. dissolving the active compound in a low-molecular alcohol which has 1 to 4 carbon atoms and is optionally substituted by up to 3 fluorine atoms or in water or in a mixture of these two solvents, mixing the solution with the poly-D-(-)-3-hydroxybutyric acid, drying the moist material and pressing the product, or
2. dissolving the poly-D(-)-3-hydroxybutyric acid in a halogenated aliphatic C_1-C_4-hydrocarbon, mixing the solution with a solution of the active compound in a low-molecular alcohol which has 1 to 4 carbon atoms and is optionally substituted by up to 3 fluorine atoms, subjecting the resulting solution to spray-drying and pressing the dried material, or
3. dissolving the poly-D(-)-3-hydroxybutyric acid in

a halogenated aliphatic C_1-C_4-hydrocarbon, suspending the active compound in this solution, pouring the suspension onto a suitable substrate, evaporating off the solvent and, if appropriate, dividing up the resulting film into pieces of suitable size.

4. The process as claimed in claim 3, wherein the pressed piece or film is comminuted in a further step and suspended in a solvent suitable for injection purposes.

5. The process as claimed in claim 3, wherein the active compound is dissolved in methanol.

6. The process as claimed in claim 3, wherein the carrier substance is dissolved in chloroform.

DATED THIS 31st day of July, 1984

HOECHST AKTIENGESLLSCHAFT

EDWD. WATERS & SONS.
PATENT ATTORNEYS,
50 QUEEN STREET,
MELBOURNE. VIC. 3000.

(12) PATENT ABRIDGEMENT (11) Document No. AU-B-31399/84
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(71) Applicant
HOECHST A.G.;

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EDWD. WATERS & SONS

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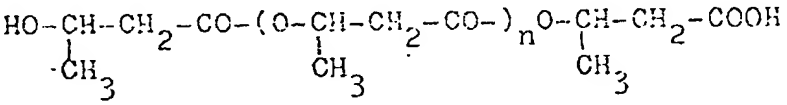

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(CONVENTION. By one or more persons and/or a Company.) Form 4

567572

COMMONWEALTH OF AUSTRALIA

Patents Act .952-1969

CONVENTION APPLICATION FOR A PATENT

(1) Here insert (in *full*) Name or Names of Applicant or Applicants, followed by Address (es).

I/We (1) HOECHST AKTIENGESELLSCHAFT,
of 45 Bruningstrasse,
D-6230 Frankfurt am Main 80,
Federal REpublic of Germany.

(2) Here insert Title of Invention.

hereby apply for the grant of a Patent for an invention entitled: (2)
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(3) Here insert number(s) of basic application(s)

which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered (3)
P 33 27 856.3 and P 33 36 197.5

(4) Here insert Name of basic Country or Countries, and basic date or dates

for a patent or similar protection made in (4) Federal Republic of Germany on 2nd August, 1983 and 5th October, 1983.

Address for Service in Australia: [illegible]
Attorney: 15-10-87

My/Our address for service is Messrs. Edwd. Waters & Sons, Patent Attorneys. 50 Queen Street, Melbourne, Victoria, Australia.

LODGED AT SUB-OFFICE
- 1 AUG 1984
Melbourne

DATED this 19th day of July, 1984

(5) Signature (s) of Applicant (s) or Seal of Company and Signatures of its Officers as prescribed by its Articles of Association

HOECHST AKTIENGESELLSCHAFT

James Murray

JAMES MURRAY

Form 7 & 8

COMMONWEALTH OF AUSTRALIA

Patents Act 1952

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We, Karl-Hermann Meyer-Dulheuer, 31 Höhenstraße, D-6242 Kronberg/Taunus, Otto Klein, 24 Johann-Strauß-Straße, D-6233 Kelkheim (Taunus); Federal Republic of Germany
do solemnly and sincerely declare as follows:

1. We are authorized by HOECHST AKTIENGESELLSCHAFT the applicant for the patent to make this declaration on its behalf.

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c) Jürgen Kurt Sandow, 22 Am Haideplacken, D-6240 Königstein/Taunus
a) - c) Federal Republic of Germany

~~is~~ are the actual inventor(s) of the invention and the facts upon which HOECHST AKTIENGESELLSCHAFT is entitled to make the application are as follows:
The said HOECHST AKTIENGESELLSCHAFT is the assignee of the said Wolfgang König, Heinz-Rüdiger Seidel and Jürgen Kurt Sandow

4. The basic applications referred to in paragraph 2 of this Declaration ~~was~~ were the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Frankfurt/Main, Federal Republic of Germany
this 16th day of July 1984

To the Commissioner of Patents

Hoechst Aktiengesellschaft

ppa. Meyer-Dulheuer i.V. Klein

Prokurist Authorized signatory

PAT 510 (ppa.Meyer-Dulheuer) (i.V.Klein)

567572

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

31399/84

Priority :

Related Art :

Name of Applicant : HOECHST AKTIENGESELLSCHAFT

Address of Applicant : 45 Bruningstrasse, D-6230 Frankfurt/Main 80, Federal REpublic of Germany.

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Address for Service : EDWD. WATERS & SONS,
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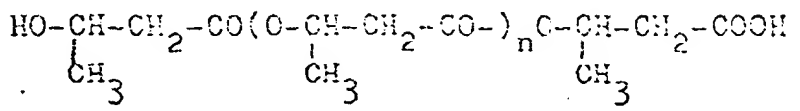
It has furthermore been reported that the peptides are released slowly from medicaments containing peptides as the active compounds and biodegradable polymers as carrier substances. The carriers are chiefly synthetic polyesters of lactic acid and copolymers of lactic acid and glycolic acid (c.f. for example, European Patent Applications publication numbers 0,052,510 and 0,058,481) and synthetic amino acid polymers (c.f. U.S. Patent 4,351,337). The disadvantage of synthetic polymers is that residues of the polymerization catalyst must be reckoned with. Such residues are undesirable in medicaments, especially in implants.

It has now been found that naturally occurring polyhydroxybutyric acid is suitable as a carrier for peptide-containing implants from which the active compound is released in a protracted manner.

The invention thus relates to implants containing regulatory peptides or analogs thereof as the active compounds and naturally occurring poly-D-(-)-3-hydroxybutyric acid (PHB) of the formula



in which n represents a number ~~between~~ from 500 ~~and~~ to 25,000, as the biologically degradable carrier.

In the statements made above and below, "peptides" means regulatory peptides and analogs thereof, as well as physiologically acceptable salts thereof.

The invention furthermore relates to processes for the preparation of implants containing regulatory peptides or analogs thereof as active compounds, which comprise

1. dissolving the active compound in a low-molecular alcohol which has 1 to 4 carbon atoms and is optionally substituted by up to 3 fluorine atoms or in water or in a mixture of these solvents, mixing the solution with the poly-D-(-)-3-hydroxybutyric acid, drying the moist material and pressing the product, or

2. dissolving the poly-D(-)-3-hydroxybutyric acid in a halogenated aliphatic C_1-C_4-hydrocarbon, mixing the solution with a solution of the active compound in a low-molecular alcohol which has 1 to 4 carbon atoms and is optionally substituted by up to 3 fluorine atoms, subjecting the resulting solution to spray-drying and

pressing the dried cottonwool-like material, or

3. dissolving the poly-D(-)-3-hydroxybutyric acid in a halogenated aliphatic C_1-C_4-hydrocarbon, suspending the active compound in this solution, pouring the suspension onto a suitable substrate, for example into a glass dish, evaporating off the solvent and, if appropriate, dividing up the resulting film into pieces of suitable size.

The resulting pressed pieces or films can be ground and divided into various particle sizes by sieving. The solid shaped articles can be implanted as such or, after prior comminution, injected in the form of suspensions.

The regulatory peptides (naturally occurring, synthetic and semi-synthetic), which can also be used in the form of salts, are soluble in water and low-molecular alcohols which are optionally substituted by fluorine. Possible alcohols are, in particular, methanol and trifluoroethanol. Particularly suitable solvents for the PHB are fluorinated and chlorinated hydrocarbons, such as methylene chloride, chloroform and 1,1,2-trichloro-1,2,2-trifluoroethane, methylene chloride and chloroform being especially suitable.

The PHB is synthesized by bacteria, such as, for example, by Alcaligenes eutrophus. It is obtained in the form of small globules in the bacteria and can be greatly increased in concentration by corresponding conditions in the bacteria and easily isolated therefrom (c.f. Pharma.

Ind. 45, pages 525-527). Each unit of PHB consists of optically pure D-(-)-3-hydroxybutyric acid.

Biological degradation of PHB in vivo proceeds relatively slowly and contributes little to the release of an active compound from an implant. The release is chiefly controlled by the surface of the implant and the amount of active compound contained therein. If very small amounts of a peptide are to be released for a relatively long time, an impant with a small surface area and a low peptide content, for example in the form of pressed pieces, is advisable. The release from the pressed piece can be further reduced by coating the implant completely or partly with a layer of PHB or other biologically degradable polymers, such as polylactic acid or polylactic acid/polyglycolic acid copolymers or with polymers such as ethylcellulose, poly(meth)acrylic acid derivatives or polydimethylsiloxanes.

An essentially uniform release of peptides for up to one year can be achieved with such impants. The implants can easily be removed by operation, if the treatment is to be discontinued.

Whilst the implantation tablets prepared according to method 1 release a relatively constant amount of a regulatory peptide from the start, the implants obtained according to method 2 release a relatively large amount of peptide in the first days and then release constant small amounts. Good adaptation to the desired pattern of release of the active compound is thus possible with the

implants according to the invention.

These slow rates of release are surprising when compared with the rates of release of about 40 days, which in contrast are rapid, obtained with the copolymers of lactic acid and glycolic acid (c.f. European Patent Application publication number 0,058,481).

Very small tablets or other small shaped articles throughout which the entire dose is distributed are suitable as implants for shorter release times. As a result of the substantially larger surface area which a large number of medicinal carriers have in comparison with a single shaped piece, the release is more rapid. Small particles which can be prepared by comminution of tablets and films are preferred. They can be injected, after suspension in a suitable medium. The particle size should not exceed a particular value here and is advantageously in the range from 0.1 to 200 µm.

Physiological saline solution in which, for example, 1% of hydroxypropylmethylcellulose (Methocel ® E5), carboxymethylcellulose (Blanose ® 7LF) or polyethylene glycol sorbitan monostearate (Tween ® 20) is dissolved can be used for suspension and injection of the particles.

Regulatory peptides are endogenous peptides which have a physiological action, they are also called peptide hormones, which, depending on the site of synthesis or release, are classified into, for example, peptide hormones of the hypothalamus, of the pituitary gland, of the

gastrointestinal tract or of the thyroid gland. This classification is inappropriate today, since it is known that the so-called peptide hormones are not produced only at one site in the body and, in addition to their endocrine mode of action, can also act in a paracrine or neurocrine manner.

Classification of these peptides according to indications is also inappropriate, since they can develop the most diverse therapeutic activities, depending on the site of action and the dose.

Examples of representative regulatory peptides which the implants according to the invention can contain are oxytocin, vasopressin, thyroliberin the anorexigenic peptide, gonadoliberin, calcitonin, parathormone the epidermal growth factor, secretin the vasoactive intestinal peptide, somatoliberin the gastrin-inhibiting or glucose-dependent insulinotropic peptide, glucagon the pancreatic spasmolytic peptide, somatostatin, bombesin the gastrin-releasing peptide, motilin, neutrotensin, substance P, sauvagin, corticoliberin, urotensin I and II, angiotensin I and II, bradykinin, corticotropin, encephalins, dynorphin, dermophin, casomorhins, gastrin, cholecystokin, cerulein, thymus factors, interferons, insulin, growth hormone and prolactin.

The highly active analogs of gonadoliberin, such as, for example, [D-Ser(Bu^t)^6]gonadoliberin-(1-9)nonapeptide-ethylamide (buserelin, Drugs of the Future 4, 1979, pages 175-77, 8, 1983, page 254), [D-Trp^6]

gonadoliberin (Drugs of the Future 3, 1978, pages 645-646), [D-Trp^6]gonadoliberin(1-9)-nonapeptide-ethylamide (Drugs of the Future 7, 1982, pages 637-642), [D-Leu^6] gonadoliberin(1-9)-nonapeptide-ethylamide (Drugs of the Future 7, 1982, pages 882-886), [D-Ser(But)^6, AzaGly^{10}] gonadoliberin (Drugs of the Future 5, 1980, pages 191-192; 8, 1983, pages 364-365), [D-Trp^6, N-MeLeu^7] gonadoliberin-(1-9)-nonapeptide-ethylamide (Drugs of the Future 8, 1983, pages 347-350), [D-α-aminoadipic acid δ-tert.-butyl ester^6] gonadoliberin-(1-9)-nonapeptide-ethylamide (German Offenlegungsschrift 3,020,941), [D-Lys(Boc)^6] gonadoliberin-(1-9)-nonapeptide-ethylamide (German Patent 2,438,350), [D-3-(2,4,6-trimethylphenyl)-Ala^6] gonadoliberin and [D-3-(2-naphthyl)-Ala^6] gonadoliberin (J. Med. Chem. 25, 1982, pages 795-801), are of particular importance.

In a high dosage, these peptides reduce the plasma levels of lutropin and follitropin and hence those of the gonadal steroids testosterone and oestradiol. These derivatives can therefore be used for hormone-dependent tumors, such as, for example, carcinoma of the prostate or of the breast, and also for endometriosis and pubertas praecox in children. Continuous uniform release of the active compound is particularly important for this therapy. With the formulation according to the invention, the necessary amount of the active compound, which would otherwise have to be administered parenterally or intranasally 2-3 times daily, can be released for weeks or months with a single administration. Use on older persons

and children is thus particularly safe from administration errors (compliance).

Another important use of the formulation according to the invention is the protracted release of somatostatin and somatostatin analogs, which can be used in all cases where somatostatin infusions exhibit an advantageous effect; for example for hemorrhages of the gastrointestinal tract, for gastric ulcers, for the treatment of tumors which produce hormones which can be inhibited by somatostatin, such as, for example, for Zollinger-Ellison syndrome or Verner-Morrison syndrome, or for tumors which produce insulin or glucagon, for hormone-dependent tumors, if the corresponding hormones can be inhibited by somatostatin, for certain types of leukemia, for metabolism disorders with increased hormone levels which can be inhibited by somatostatin, such as, for example, rheumatoid arthritis, where the plasma insulin and growth hormone are too high, for acromegaly or psoriasis, for Diabetes mellitus (inhibition of glucagon), for chondrosarcoma and for states of shock.

Highly active analogs of somatostatin are compounds in which, for example, Trp^8 is replaced by D-Trp or 5-F-D-Trp, or shortened cyclic compounds, such as, for example,

cyclo-Pro-Phe-D-Trp-Lys-Thr-Phe

(Nature 292, 1981, page 55) or

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol

(Life Sci. 31, 1982, pages 1,133-1,140).

Therapy of upper gastrointestinal hemorrhages with secretin infusions can also be simplified by the new galenical formulation.

The ratio of active compound to carrier material can vary within wide limits. Since the peptides are administered in low dosages, the amount of carrier material in the implants is relatively high (for example 100 : 1 to 10,000 : 1).

Example 1:

2.5 g of PHB were moistened with a methanolic solution containing 2.875 mg of buserelin acetate (corresponding to 2.5 mg of buserelin) and mixed thoroughly. The moist material was dried in vacuo, with shaking. The procedure was repeated several times with pure methanol. The dry mixture was pressed to tablets (implants) weighing 50 mg and containing 50 µg of buserelin.

Example 2:

2.875 mg of buserelin acetate (corresponding to 2.5 mg of buserelin) were dissolved in 30 ml of methanol, and 2.5 g of PHB were dissolved in 70 ml of chloroform. The two solutions were combined and subjected to spray-drying. A flaky powder was obtained, from which tablets weighing 50 mg and containing 50 µg of buserelin were pressed.

Example 3:

The pressed pieces prepared under Example 1 or 2 were micronized. The resulting particles were divided into particle size ranges up to about 200 µm by sieving. The fractions were suspended in physiological saline solution with 1% of carboxymethylcellulose in a concentration of 50 mg/ml for injection.

Example 4:

2.5 g of PHB were dissolved in 25 g of chloroform. 287.5 mg of buserelin acetate (corresponding to 250 mg of buserelin) were suspended in this solution. The suspension was poured into a Petri dish. The solvent was allowed to evaporate slowly. A film was formed, and divided into flakes 1 cm^2 in size, containing about 5 mg of buserelin.

Example 5:

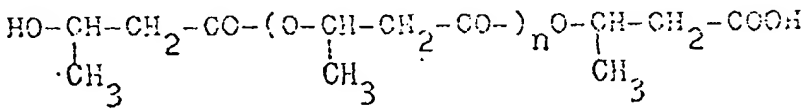
Biological testing of the formulations on rats

Two implantation materials of PHB and a copolymer of lactic acid and glycolic acid (PLG) of identical weight and size which had been prepared analogously to Example 1 were investigated. The materials were tested on adult rats weighing 400 g, the amount of peptide released each day being determined by pharmacokinetic detection by means of specific radioimmunoassay. In the case of the PHB implant, a release of 0.203 ± 0.038 ng of buserelin per day was found. In contrast, a release of 1.075 ± 0.029 ng of buserelin/day was found for the PLG implant. The total duration of the release of the peptide

was calculated from the cumulative rate of release. It is 221 ± 29 days for the PHB implant and 46.5 ± 1.2 days for the PLG implant. The PHB implant material is thus considerably more suitable for long-term release of peptides than the copolymer of lactic acid and glycolic acid (50:50) used for comparison.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An implant containing a regulatory peptide or one of its analogs as the active compound and naturally occurring poly-D(-)-3-hydroxybutyric acid of the formula



in which n represents a number from 500 to 25,000, as the biologically degradable carrier.

2. Implant as claimed in claim 1, which contains buserelin(acetate) as the active compound.

3. A process for the preparation of an implant as claimed in claim 1, which comprises

1. dissolving the active compound in a low-molecular alcohol which has 1 to 4 carbon atoms and is optionally substituted by up to 3 fluorine atoms or in water or in a mixture of these two solvents, mixing the solution with the poly-D-(-)-3-hydroxybutyric acid, drying the moist material and pressing the product, or
2. dissolving the poly-D(-)-3-hydroxybutyric acid in a halogenated aliphatic C_1-C_4-hydrocarbon, mixing the solution with a solution of the active compound in a low-molecular alcohol which has 1 to 4 carbon atoms and is optionally substituted by up to 3 fluorine atoms, subjecting the resulting solution to spray-drying and pressing the dried material, or
3. dissolving the poly-D(-)-3-hydroxybutyric acid in

a halogenated aliphatic C_1-C_4-hydrocarbon, suspending the active compound in this solution, pouring the suspension onto a suitable substrate, evaporating off the solvent and, if appropriate, dividing up the resulting film into pieces of suitable size.

4. The process as claimed in claim 3, wherein the pressed piece or film is comminuted in a further step and suspended in a solvent suitable for injection purposes.

5. The process as claimed in claim 3, wherein the active compound is dissolved in methanol.

6. The process as claimed in claim 3, wherein the carrier substance is dissolved in chloroform.

DATED THIS 31st day of July, 1984

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(12) AUSTRALIAN PATENT ABSTRACT
(19) AU (11) AU-A-31399/84

(54) REGULATORY PEPTIDE IN POLY HYDROXYBUTYRIC ACID AS A BIODEGRADABLE CARRIER

(71) HOECHST AKTIENGESELLSCHAFT

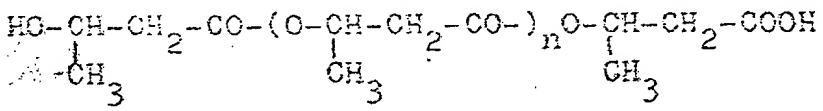
(21) 31399/84 (22) 1.8.84 (24) 2.8.83
(31) 332856 (32) 2.8.83 (33) DE
3336197 5.10.83 DE

(43) 6.2.85
(51)[3] A61K 47/00 A61K 37/02
(72) NOT GIVEN
(74) WM

(57) Implant includes tablets, flakes and injections

Claim

1. An implant containing a regulatory peptide or one of its analogs as the active compound and naturally occurring poly-D(-)-3-hydroxybutyric acid of the formula



in which n represents a number between 500 and 25,000, as the biologically degradable carrier.

Form 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority :

Related Art .

Name of Applicant : HOECHST AKTIENGESELLSCHAFT

Address of Applicant : 45 Bruningstrasse, D-6230 Frankfurt/Main 80, Federal REpublic of Germany.

Actual Inventor:

Address for Service : EDWD. WATERS & SONS,
50 QUEEN STREET, MELBOURNE, AUSTRALIA, 3000.

Complete Specification for the invention entitled:

PHARMACEUTICAL PRODUCTS WITH PROTRACTED RELEASE WHICH CONTAIN REGULATORY PEPTIDES, AND PROCESSES FOR THEIR PREPARATION

The following statement is a full description of this invention, including the best method of performing it known to :

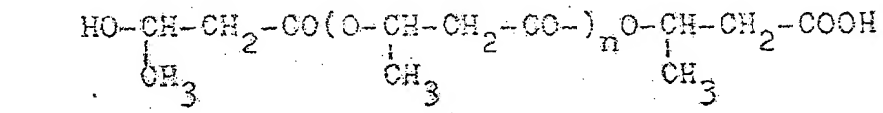
The invention relates to a formulation, which can be implanted, of regulatory peptides and of analogs thereof with protracted release, and to processes for the preparation of the implants.

It has already been reported that, during in vitro experiments, the active compound is released slowly from matrix tablets containing 7-hydroxyethyltheophylline, as the active compound, and poly-D(-)-3-hydroxybutyric acid, as the biologically degradable carrier material (Pharm. Ind. 45, pages 525-527 (1983)).

It has furthermore been reported that the peptides are released slowly from medicaments containing peptides as the active compounds and biodegradable polymers as carrier substances. The carriers are chiefly synthetic polyesters of lactic acid and copolymers of lactic acid and glycolic acid (c.f. for example, European Patent Applications publication numbers 0,052,510 and 0,058,481) and synthetic amino acid polymers (c.f. U.S. Patent 4,351,337). The disadvantage of synthetic polymers is that residues of the polymerization catalyst must be reckoned with. Such residues are undesirable in medicaments, especially in implants.

It has now been found that naturally occurring polyhydroxybutyric acid is suitable as a carrier for peptide-containing implants from which the active compound is released in a protracted manner.

The invention thus relates to implants containing regulatory peptides or analogs thereof as the active compounds and naturally occurring poly-D-(-)-3-hydroxybutyric acid (PHB) of the formula



in which n represents a number between 500 and 25,000, as the biologically degradable carrier.

In the statements made above and below, "peptides" means regulatory peptides and analogs thereof, as well as physiologically acceptable salts thereof.

The invention furthermore relates to processes for the preparation of implants containing regulatory peptides or analogs thereof as active compounds, which comprise

1. dissolving the active compound in a low-molecular alcohol which has 1 to 4 carbon atoms and is optionally substituted by up to 3 fluorine atoms or in water or in a mixture of these solvents, mixing the solution with the poly-D-(-)-3-hydroxybutyric acid, drying the moist material and pressing the product, or

2. dissolving the poly-D(-)-3-hydroxybutyric acid in a halogenated aliphatic C_1-C_4-hydrocarbon, mixing the solution with a solution of the active compound in a low-molecular alcohol which has 1 to 4 carbon atoms and is optionally substituted by up to 3 fluorine atoms, subjecting the resulting solution to spray-drying and

pressing the dried cottonwool-like material, or

3. dissolving the poly-D(-)-3-hydroxybutyric acid in a halogenated aliphatic C_1-C_4-hydrocarbon, suspending the active compound in this solution, pouring the suspension onto a suitable substrate, for example into a glass dish, evaporating off the solvent and, if appropriate, dividing up the resulting film into pieces of suitable size.

The resulting pressed pieces or films can be ground and divided into various particle sizes by sieving. The solid shaped articles can be implanted as such or, after prior comminution, injected in the form of suspensions.

The regulatory peptides (naturally occurring, synthetic and semi-synthetic), which can also be used in the form of salts, are soluble in water and low-molecular alcohols which are optionally substituted by fluorine. Possible alcohols are, in particular, methanol and trifluoroethanol. Particularly suitable solvents for the PHB are fluorinated and chlorinated hydrocarbons, such as methylene chloride, chloroform and 1,1,2-trichloro-1,2,3-trifluoroethane, methylene chloride and chloroform being especially suitable.

The PHB is synthesized by bacteria, such as, for example, by Alcaligenes eutrophus. It is obtained in the form of small globules in the bacteria and can be greatly increased in concentration by corresponding conditions in the bacteria and easily isolated therefrom (c.f. Pharma.

Ind. 45, pages 525-527). Each unit of PHB consists of optically pure D-(-)-3-hydroxybutyric acid.

Biological degradation of PHB in vivo proceeds relatively slowly and contributes little to the release of an active compound from an implant. The release is chiefly controlled by the surface of the implant and the amount of active compound contained therein. If very small amounts of a peptide are to be released for a relatively long time, an impant with a small surface area and a low peptide content, for example in the form of pressed pieces, is advisable. The release from the pressed piece can be further reduced by coating the implant completely or partly with a layer of PHB or other biologically degradable polymers, such as polylactic acid or polylactic acid/polyglycolic acid copolymers or with polymers such as ethylcellulose, poly(meth)acrylic acid derivatives or polydimethylsiloxanes.

An essentially uniform release of peptides for up to one year can be achieved with such impants. The implants can easily be removed by operation, if the treatment is to be discontinued.

Whilst the implantation tablets prepared according to method 1 release a relatively constant amount of a regulatory peptide from the start, the implants obtained according to method 2 release a relatively large amount of peptide in the first days and then release constant small amounts. Good adaptation to the desired pattern of release of the active compound is thus possible with the

implants according to the invention.

These slow rates of release are surprising when compared with the rates of release of about 40 days, which in contrast are rapid, obtained with the copolymers of lactic acid and glycolic acid (c.f. European Patent Application publication number 0,058,481).

Very small tablets or other small shaped articles throughout which the entire dose is distributed are suitable as implants for shorter release times. As a result of the substantially larger surface area which a large number of medicinal carriers have in comparison with a single shaped piece, the release is more rapid. Small particles which can be prepared by comminution of tablets and films are preferred. They can be injected, after suspension in a suitable medium. The particle size should not exceed a particular value here and is advantageously in the range from 0.1 to 200 µm.

Physiological saline solution in which, for example, 1% of hydroxypropylmethylcellulose (Methocel R E5), carboxymethylcellulose (Blanose R 7LF) or polyethylene glycol sorbitan monostearate (Tween R 20) is dissolved can be used for suspension and injection of the particles.

Regulatory peptides are endogenous peptides which have a physiological action, they are also called peptide hormones, which, depending on the site of synthesis or release, are classified into, for example, peptide hormones of the hypothalamus, of the pituitary gland, of the

gastrointestinal tract or of the thyroid gland. This classification is inappropriate today, since it is known that the so-called peptide hormones are not produced only at one site in the body and, in addition to their endocrine mode of action, can also act in a paracrine or neurocrine manner.

Classification of these peptides according to indications is also inappropriate, since they can develop the most diverse therapeutic activities, depending on the site of action and the dose.

Examples of representative regulatory peptides which the implants according to the invention can contain are oxytocin, vasopressin, thyroliberin the anorexigenic peptide, gonadoliberin, calcitonin, parathormone the epidermal growth factor, secretin the vasoactive intestinal peptide, somatoliberin the gastrin-inhibiting or glucose-dependent insulinotropic peptide, glucagon the pancreatic spasmolytic peptide, somatostatin, bombesin the gastrin-releasing peptide, motilin, neutrotensin, substance P, sauvagin, corticoliberin, urotensin I and II, angiotensin I and II, bradykinin, corticotropin, encephalins, dynorphin, dermophin, casomorhins, gastrin, cholecystokin, cerulein, thymus factors, interferons, insulin, growth hormone and prolactin.

The highly active analogs of gonadoliberin, such as, for example, [D-Ser(Bu^t)^6]gonadoliberin-(1-9)nonapeptide-ethylamide (buserelin, Drugs of the Future 4, 1979, pages 175-77, 8, 1983, page 254), [D-Trp^6]

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In a high dosage, these peptides reduce the plasma levels of lutropin and follitropin and hence those of the gonadal steroids testosterone and oestradiol. These derivatives can therefore be used for hormone-dependent tumors, such as, for example, carcinoma of the prostate or of the breast, and also for endometriosis and pubertas praecox in children. Continuous uniform release of the active compound is particularly important for this therapy. With the formulation according to the invention, the necessary amount of the active compound, which would otherwise have to be administered parenterally or intranasally 2-3 times daily, can be released for weeks or months with a single administration. Use on older persons

and children is thus particularly safe from administration errors (compliance).

Another important use of the formulation according to the invention is the protracted release of somatostatin and somatostatin analogs, which can be used in all cases where somatostatin infusions exhibit an advantageous effect, for example for hemorrhages of the gastrointestinal tract, for gastric ulcers, for the treatment of tumors which produce hormones which can be inhibited by somatostatin, such as, for example, for Zollinger-Ellison syndrome or Werner-Morrison syndrome, or for tumors which produce insulin or glucagon, for hormone-dependent tumors, if the corresponding hormones can be inhibited by somatostatin, for certain types of leukemia, for metabolism disorders with increased hormone levels which can be inhibited by somatostatin, such as, for example, rheumatoid arthritis, where the plasma insulin and growth hormone are too high, for acromegaly or psoriasis, for Diabetes mellitus (inhibition of glucagon), for chondrosarcoma and for states of shock.

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Therapy of upper gastrointestinal hemorrhages with secretin infusions can also be simplified by the new galenical formulation.

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Example 1:

2.5 g of PHB were moistened with a methanolic solution containing 2.875 mg of buserelin acetate (corresponding to 2.5 mg of buserelin) and mixed thoroughly. The moist material was dried in vacuo, with shaking. The procedure was repeated several times with pure methanol. The dry mixture was pressed to tablets (implants) weighing 50 mg and containing 50 µg of buserelin.

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2.875 mg of buserelin acetate (corresponding to 2.5 mg of buserelin) were dissolved in 30 ml of methanol, and 2.5 g of PHB were dissolved in 70 ml of chloroform. The two solutions were combined and subjected to spray-drying. A flaky powder was obtained, from which tablets weighing 50 mg and containing 50 µg of buserelin were pressed.

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The pressed pieces prepared under Example 1 or 2 were micronized. The resulting particles were divided into particle size ranges up to about 200 µm by sieving. The fractions were suspended in physiological saline solution with 1% of carboxymethylcellulose in a concentration of 50 mg/ml for injection.

Example 4:

2.5 g of PHB were dissolved in 25 g of chloroform. 287.5 mg of buserelin acetate (corresponding to 250 mg of buserelin) were suspended in this solution. The suspension was poured into a Petri dish. The solvent was allowed to evaporate slowly. A film was formed, and divided into flakes 1 cm^2 in size, containing about 5 mg of buserelin.

Example 5:

Biological testing of the formulations on rats

Two implantation materials of PHB and a copolymer of lactic acid and glycolic acid (PLG) of identical weight and size which had been prepared analogously to Example 1 were investigated. The materials were tested on adult rats weighing 400 g, the amount of peptide released each day being determined by pharmacokinetic detection by means of specific radioimmunoassay. In the case of the PHB implant, a release of 0.203 ± 0.038 ng of buserelin per day was found. In contrast, a release of 1.075 ± 0.029 ng of buserelin/day was found for the PLG implant. The total duration of the release of the peptide

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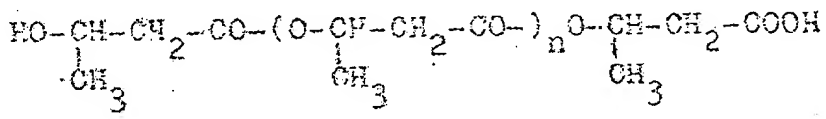
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An implant containing a regulatory peptide or one of its analogs as the active compound and naturally occurring poly-D(-)-3-hydroxybutyric acid of the formula



in which n represents a number between 500 and 25,000, as the biologically degradable carrier.

2. Implant as claimed in claim 1, which contains buserelin(acetate) as the active compound.

3. A process for the preparation of an implant as claimed in claim 1, which comprises

1. dissolving the active compound in a low-molecular alcohol which has 1 to 4 carbon atoms and is optionally substituted by up to 3 fluorine atoms or in water or in a mixture of these two solvents, mixing the solution with the poly-D-(-)-3-hydroxybutyric acid, drying the moist material and pressing the product, or
2. dissolving the poly-D(-)-3-hydroxybutyric acid in a halogenated aliphatic C_1-C_4-hydrocarbon, mixing the solution with a solution of the active compound in a low-molecular alcohol which has 1 to 4 carbon atoms and is optionally substituted by up to 3 fluorine atoms, subjecting the resulting solution to spray-drying and pressing the dried material, or
3. dissolving the poly-D(-)-3-hydroxybutyric acid in

a halogenated aliphatic C_1-C_4-hydrocarbon, suspending the active compound in this solution, pouring the suspension onto a suitable substrate, evaporating off the solvent and, if appropriate, dividing up the resulting film into pieces of suitable size.

4. The process as claimed in claim 3, wherein the pressed piece or film is comminuted in a further step and suspended in a solvent suitable for injection purposes.

5. The process as claimed in claim 3, wherein the active compound is dissolved . methanol.

6. The process as claimed in claim 3, wherein the carrier substance is dissolved in chloroform.

DATED THIS 31st day of July, 1984

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(12) AUSTRALIAN PATENT ABSTRACT
(19) AU (11) AU-A-31399/84

(54) REGULATORY PEPTIDE IN POLY HYDROXYBUTYRIC ACID AS A BIODEGRADABLE CARRIER

(71) HOECHST AKTIENGESELLSCHAFT
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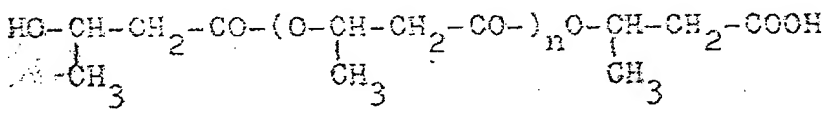
(31) 332/856 (32) 2.8.83 (33) DE
3336197 5.10.83 DE
(43) [illegible].8.85
(51)[3] A61K 47/00 A61K 37/02
(72) NOT GIVEN
(74) WM

(57) Implant includes tablets, flakes and injections

Claim

1. An implant containing a regulatory peptide or one of its analogs as the active compound and naturally occurring poly-D(-)-3-hydroxybutyric acid of the formula



in which n represents a number between 500 and 25,000, as the biologically degradable carrier.

Form 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority :

Related Art .

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Complete Specification for the invention entitled:

PHARMACEUTICAL PRODUCTS WITH PROTRACTED RELEASE WHICH CONTAIN REGULATORY PEPTIDES, AND PROCESSES FOR THEIR PREPARTATION

The following statement is a full description of this invention, including the best method of performing it known to :

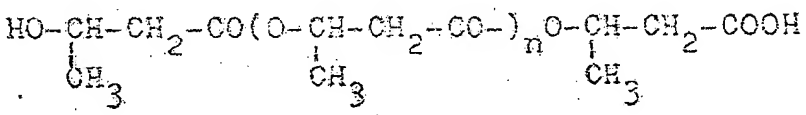
The invention relates to a formulation, which can be implanted, of regulatory peptides and of analogs thereof with protracted release, and to processes for the preparation of the implants.

It has already been reported that, during in vitro experiments, the active compound is released slowly from matrix tablets containing 7-hydroxyethyltheophylline, as the active compound, and poly-D(-)-3-hydroxybutyric acid, as the biologically degradable carrier material (Pharm. Ind. 45, pages 525-527 (1983)).

It has furthermore been reported that the peptides are released slowly from medicaments containing peptides as the active compounds and biodegradable polymers as carrier substances. The carriers are chiefly synthetic polyesters of lactic acid and copolymers of lactic acid and glycolic acid (c.f. for example, European Patent Applications publication numbers 0,052,510 and 0,058,481) and synthetic amino acid polymers (c.f. U.S. Patent 4,351,337). The disadvantage of synthetic polymers is that residues of the polymerization catalyst must be reckoned with. Such residues are undesirable in medicaments, especially in implants.

It has now been found that naturally occurring polyhydroxybutyric acid is suitable as a carrier for peptide-containing implants from which the active compound is released in a protracted manner.

The invention thus relates to implants containing regulatory peptides or analogs thereof as the active compounds and naturally occurring poly-D-(-)-3-hydroxybutyric acid (PHB) of the formula



in which n represents a number between 500 and 25,000, as the biologically degradable carrier.

In the statements made above and below, "peptides" means regulatory peptides and analogs thereof, as well as physiologically acceptable salts thereof.

The invention furthermore relates to processes for the preparation of implants containing regulatory peptides or analogs thereof as active compounds, which comprise

1. dissolving the active compound in a low-molecular alcohol which has 1 to 4 carbon atoms and is optionally substituted by up to 3 fluorine atoms or in water or in a mixture of these solvents, mixing the solution with the poly-D-(-)-3-hydroxybutyric acid, drying the moist material and pressing the product, or

2. dissolving the poly-D(-)-3-hydroxybutyric acid in a halogenated aliphatic C_1-C_4-hydrocarbon, mixing the solution with a solution of the active compound in a low-molecular alcohol which has 1 to 4 carbon atoms and is optionally substituted by up to 3 fluorine atoms, subjecting the resulting solution to spray-drying and

pressing the dried cottonwool-like material, or

3. dissolving the poly-D(-)-3-hydroxybutyric acid in a halogenated aliphatic C_1-C_4-hydrocarbon, suspending the active compound in this solution, pouring the suspension onto a suitable substrate, for example into a glass dish, evaporating off the solvent and, if appropriate, dividing up the resulting film into pieces of suitable size.

The resulting pressed pieces or films can be ground and divided into various particle sizes by sieving. The solid shaped articles can be implanted as such or, after prior comminution, injected in the form of suspensions.

The regulatory peptides (naturally occurring, synthetic and semi-synthetic), which can also be used in the form of salts, are soluble in water and low-molecular alcohols which are optionally substituted by fluorine. Possible alcohols are, in particular, methanol and trifluoroethanol. Particularly suitable solvents for the PHB are fluorinated and chlorinated hydrocarbons, such as methylene chloride, chloroform and 1,1,2-trichloro-1,2,3-trifluoroethane, methylene chloride and chloroform being especially suitable.

The PHB is synthesized by bacteria, such as, for example, by Alcaligenes eutrophus. It is obtained in the form of small globules in the bacteria and can be greatly increased in concentration by corresponding conditions in the bacteria and easily isolated therefrom (c.f. Pharma.

Ind. 45, pages 525-527). Each unit of PHB consists of optically pure D-(-)-3-hydroxybutyric acid.

Biological degradation of PHB in vivo proceeds relatively slowly and contributes little to the release of an active compound from an implant. The release is chiefly controlled by the surface of the implant and the amount of active compound contained therein. If very small amounts of a peptide are to be released for a relatively long time, an impant with a small surface area and a low peptide content, for example in the form of pressed pieces, is advisable. The release from the pressed piece can be further reduced by coating the implant completely or partly with a layer of PHB or other biologically degradable polymers, such as polylactic acid or polylactic acid/polyglycolic acid copolymers or with polymers such as ethylcellulose, poly(meth)acrylic acid derivatives or polydimethylsiloxanes.

An essentially uniform release of peptides for up to one year can be achieved with such impants. The implants can easily be removed by operation, if the treatment is to be discontinued.

Whilst the implantation tablets prepared according to method 1 release a relatively constant amount of a regulatory peptide from the start, the implants obtained according to method 2 release a relatively large amount of peptide in the first days and then release constant small amounts. Good adaptation to the desired pattern of release of the active compound is thus possible with the

implants according to the invention.

These slow rates of release are surprising when compared with the rates of release of about 40 days, which in contrast are rapid, obtained with the copolymers of lactic acid and glycolic acid (c.f. European Patent Application publication number 0,058,481).

Very small tablets or other small shaped articles throughout which the entire dose is distributed are suitable as implants for shorter release times. As a result of the substantially larger surface area which a large number of medicinal carriers have in comparison with a single shaped piece, the release is more rapid. Small particles which can be prepared by comminution of tablets and films are preferred. They can be injected, after suspension in a suitable medium. The particle size should not exceed a particular value here and is advantageously in the range from 0.1 to 200 µm.

Physiological saline solution in which, for example, 1% of hydroxypropylmethylcellulose (Methocel ^{R} E5), carboxymethylcellulose (Blanose ^{R} 7LF) or polyethylene glycol sorbitan monostearate (Tween ^{R} 20) is dissolved can be used for suspension and injection of the particles.

Regulatory peptides are endogenous peptides which have a physiological action, they are also called peptide hormones, which, depending on the site of synthesis or release, are classified into, for example, peptide hormones of the hypothalamus, of the pituitary gland, of the

gastrointestinal tract or of the thyroid gland. This classification is inappropriate today, since it is known that the so-called peptide hormones are not produced only at one site in the body and, in addition to their endocrine mode of action, can also act in a paracrine or neurocrine manner.

Classification of these peptides according to indications is also inappropriate, since they can develop the most diverse therapeutic activities, depending on the site of action and the dose.

Examples of representative regulatory peptides which the implants according to the invention can contain are oxytocin, vasopressin, thyroliberin the anorexigenic peptide, gonadoliberin, calcitonin, parathormone the epidermal growth factor, secretin the vasoactive intestinal peptide, somatoliberin the gastrin-inhibiting or glucose-dependent insulinotropic peptide, glucagon the pancreatic spasmolytic peptide, somatostatin, bombesin the gastrin-releasing peptide, motilin, neutrotensin, substance P, sauvagin, corticoliberin, urotensin I and II, angiotensin I and II, bradykinin, corticotropin, encephalins, dynorphin, dermophin, casomorhins, gastrin, cholecystokin, cerulein, thymus factors, interferons, insulin, growth hormone and prolactin.

The highly active analogs of gonadoliberin, such as, for example, [D-Ser(Bu^t)^6]gonadoliberin-(1-9)nonapeptide-ethylamide (buserelin, Drugs of the Future 4, 1979, pages 175-77, 8, 1983, page 254), [D-Trp^6]

gonadoliberin (Drugs of the Future 3, 1978, pages 645-646), [D-Trp^6]gonadoliberin(1-9)-nonapeptide-ethylamide (Drugs of the Future 7, 1982, pages 637-642), [D-Leu^6] gonadoliberin(1-9)-nonapeptide-ethylamide (Drugs of the Future 7, 1982, pages 882-886), [D-Ser(But)^6, Azagly^{10}] gonadoliberin (Drugs of the Future 5, 1980, pages 191-192; 8, 1983, pages 364-365), [D-Trp^6, N-MeLeu^7] gonadoliberin-(1-9)-nonapeptide-ethylamide (Drugs of the Future 8, 1983, pages 347-350), [D-X-aminoadipic acid δ-tert.-butyl ester^6] gonadoliberin-(1-9)-nonapeptide-ethylamide (German Offenlegungsschrift 3,020,244), [D-Lys(Boc)^6] gonadoliberin-(1-9)-nonapeptide-ethylamide (German Patent 2,438,350), [D-3-(2,4,6-trimethylphenyl)-Ala^6] gonadoliberin and [D-3-(2-naphthyl)-Ala^6] gonadoliberin (J. med. Chem. 25, 1982, pages 795-801), are of particular importance.

In a high dosage, these peptides reduce the plasma levels of lutropin and follitropin and hence those of the gonadal steroids testosterone and oestradiol. These derivatives can therefore be used for hormone-dependent tumors, such as, for example, carcinoma of the prostate or of the breast, and also for endometriosis and pubertas praecox in children. Continuous uniform release of the active compound is particularly important for this therapy. With the formulation according to the invention, the necessary amount of the active compound, which would otherwise have to be administered parenterally or intranasally 2-3 times daily, can be released for weeks or months with a single administration. Use on older persons

and children is thus particularly safe from administration errors (compliance).

Another important use of the formulation according to the invention is the protracted release of somatostatin and somatostatin analogs, which can be used in all cases where somatostatin infusions exhibit an advantageous effect, for example for hemorrhages of the gastrointestinal tract, for gastric ulcers, for the treatment of tumors which produce hormones which can be inhibited by somatostatin, such as, for example, for Zollinger-Ellison syndrome or Verner-Morrison syndrome, or for tumors which produce insulin or glucagon, for hormone-dependent tumors, if the corresponding hormones can be inhibited by somatostatin, for certain types of leukemia, for metabolism disorders with increased hormone levels which can be inhibited by somatostatin, such as, for example, rheumatoid arthritis, where the plasma insulin and growth hormone are too high, for acromegaly or psoriasis, for Diabetes mellitus (inhibition of glucagon), for chondrosarcoma and for states of shock.

Highly active analogs of somatostatin are compounds in which, for example, Trp^8 is replaced by D-Trp or 5-F-D-Trp, or shortened cyclic compounds, such as, for example,

cyclo-Pro-Phe-D-Trp-Lys-Thr-Phe

(Nature 292, 1981, page 55) or

H-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol

(Life Sci. 31, 1982, pages 1,133-1,140).

Therapy of upper gastrointestinal hemorrhages with secretin infusions can also be simplified by the new galenical formulation.

The ratio of active compound to carrier material can vary within wide limits. Since the peptides are administered in low dosages, the amount of carrier material in the implants is relatively high (for example 100 : 1 to 10,000 : 1).

Example 1:

2.5 g of PHB were moistened with a methanolic solution containing 2.875 mg of buserelin acetate (corresponding to 2.5 mg of buserelin) and mixed thoroughly. The moist material was dried in vacuo, with shaking. The procedure was repeated several times with pure methanol. The dry mixture was pressed to tablets (implants) weighing 50 mg and containing 50 µg of buserelin.

Example 2:

2.875 mg of buserelin acetate (corresponding to 2.5 mg of buserelin) were dissolved in 30 ml of methanol, and 2.5 g of PHB were dissolved in 70 ml of chloroform. The two solutions were combined and subjected to spray-drying. A flaky powder was obtained, from which tablets weighing 50 mg and containing 50 µg of buserelin were pressed.

Example 3:

The pressed pieces prepared under Example 1 or 2 were micronized. The resulting particles were divided into particle size ranges up to about 200 µm by sieving. The fractions were suspended in physiological saline solution with 1% of carboxymethylcellulose in a concentration of 50 mg/ml for injection.

Example 4:

2.5 g of PHB were dissolved in 25 g of chloroform. 287.5 mg of buserelin acetate (corresponding to 250 mg of buserelin) were suspended in this solution. The suspension was poured into a Petri dish. The solvent was allowed to evaporate slowly. A film was formed, and divided into flakes 1 cm^2 in size, containing about 5 mg of buserelin.

Example 5:

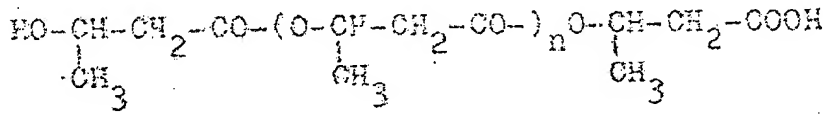
Biological testing of the formulations on rats

Two implantation materials of PHB and a copolymer of lactic acid and glycolic acid (PLG) of identical weight and size which had been prepared analogously to Example 1 were investigated. The materials were tested on adult rats weighing 400 g, the amount of peptide released each day being determined by pharmacokinetic detection by means of specific radioimmunoassay. In the case of the PHB implant, a release of 0.203 ± 0.038 ng of buserelin per day was found. In contrast, a release of 1.075 ± 0.029 ng of buserelin/day was found for the PLG implant. The total duration of the release of the peptide

was calculated from the cumulative rate of release. It is 221 ± 29 days for the PHB implant and 46.5 ± 1.2 days for the PLG implant. The PHB implant material is thus considerably more suitable for long-term release of peptides than the copolymer of lactic acid and glycolic acid (50:50) used for comparison.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:
~~XXXEXXXXXXXXXXX~~

1. An implant containing a regulatory peptide or one of its analogs as the active compound and naturally occurring poly-D(-)-3-hydroxybutyric acid of the formula



in which n represents a number between 500 and 25,000, as the biologically degradable carrier.

2. Implant as claimed in claim 1, which contains buserelin(acetate) as the active compound.

3. A process for the preparation of an implant as claimed in claim 1, which comprises

1. dissolving the active compound in a low-molecular alcohol which has 1 to 4 carbon atoms and is optionally substituted by up to 3 fluorine atoms or in water or in a mixture of these two solvents, mixing the solution with the poly-D-(-)-3-hydroxybuty.ic acid, drying the moist material and pressing the product, or
2. dissolving the poly-D(-)-3-hydroxybutyric acid in a halogenated aliphatic C_1-C_4-hydrocarbon, mixing the solution with a solution of the active compound in a low-molecular alcohol which has 1 to 4 carbon atoms and is optionally substituted by up to 3 fluorine atoms, subjecting the resulting solution to spray-drying and pressing the dried material, or
3. dissolving the poly-D(-)-3-hydroxybutyric acid in

a halogenated aliphatic C_1-C_4-hydrocarbon, suspending the active compound in this solution, pouring the suspension onto a suitable substrate, evaporating off the solvent and, if appropriate, dividing up the resulting film into pieces of suitable size.

4. The process as claimed in claim 3, wherein the pressed piece or film is comminuted in a further step and suspended in a solvent suitable for injection purposes.

5. The process as claimed in claim 3, wherein the active compound is dissolved . methanol.

6. The process as claimed in claim 3, wherein the carrier substance is dissolved in chloroform.

DATED THIS 31st day of July, 1984

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